Stanford study links cancer to loss of protein that hooks skin cells together

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In a study to be published online Oct. 21 in *PLoS Genetics*, researchers at the Stanford University School of Medicine have implicated the lack of a protein important in hooking our skin cells together in the most common variety of skin cancer. Depletion of this protein, called Perp, could be an early indicator of skin cancer development, and could be useful for staging and establishing prognoses.

These findings' significance may extend beyond skin cancer, as Perp is found in the linings of many of our internal organs, where it plays the same role it does in the skin: maintaining cell-to-cell adherence. This suggests that Perp could be a useful tool for classifying tumors in these internal organs, which are often diagnosed too late to be effectively treated.

Skin is the largest organ in the body by weight, consisting of several sheets of cells layered one atop the next. The bottom layer is composed of basal cells, which, after proliferating for a while, migrate upward toward the skin surface, differentiating from one cell type to another several times along the way. Skin's outermost layer consists mainly of closely knit squamous cells. Perp is a critical player in maintaining this cell-cell adhesion in these cell types, which makes our skin such an effective barrier against pathogens and toxic and allergenic substances.

Skin belongs to a class of tissues known collectively as epithelium. Epithelial tissue also lines many internal organs such as the lungs, colon, breast, esophagus and pancreas. Several organs' epithelial linings, like

skin, are multilayered.

"A good 90 percent of all human cancers originate in epithelial tissue," noted Laura Attardi, PhD, senior author of the study and associate professor of radiation oncology and of genetics at the medical school. "Epithelial tissues are constantly regenerating, creating ample opportunities for errors to occur during DNA replication that can promote tumor growth. Also, these tissues are particularly exposed to the environment — the skin to UV radiation, the colon to dietary carcinogens, the lungs to inhaled toxins, and so forth."

Perp, first identified by Attardi in the late 1990s, is a key protein in desmosomes, multi-protein structures found on the surfaces of epithelial cells. Desmosomes are one kind of so-called adhesion junction, cell-surface features that bind fiercely to one another from one cell to the next. Adhesion junctions cause cells to stick together and form a barrier.

Perp, a desmosomal component, weaves in and out of a cell's surface like a thread through fabric. The protein's intercellular tail wraps around structures in the cell, firmly anchoring the desmosome on the membrane. The desmosome's outward-facing features bind strongly to their counterparts on neighboring cells, creating a tight seal.

"People have long assumed that this was desmosomes' only function," said Attardi, who is also a member of the Stanford Cancer Center. The new study shows not only that desmosomes are crucial to maintaining epithelial tissues' integrity, but that the loss of Perp, which is crucial to desmosomes' function, promotes cancer. Disrupted function of another kind of adhesion junction has, indeed, been implicated in late-stage cancers. But desmosome disturbances may occur earlier on, during tumors' initial development.

In 2005, in a study published in Cell, Attardi first showed that Perp is

integral to desmosomes. She and her associates produced mice lacking Perp, allowing them, unexpectedly, to identify a role that Perp plays in the skin. Mice whose skin was deficient in Perp exhibited desmosome loss as well as blistering and increased skin-cell proliferation. In these mice, moreover, so-called p53 tumor suppression — a mechanism widely acclaimed for its importance in shutting down cell division when genetic damage can't be properly repaired — fails to function normally, implying that Perp played some as-yet-unspecified role in that pathway. (The p53 protein has been found to be mutated in at least half of all human tumors.)

"In this new study, we attempted to mimic the way skin cancers originate in people," said Attardi. She and her colleagues exposed both normal mice and the bioengineered Perp-deficient mice to UVB light — a range of ultraviolet wavelengths known to induce the great majority of human skin cancers — and compared the incidence of squamous-cell carcinoma in the two groups. In the mice lacking Perp, skin tumors arose faster, and were both more abundant and aggressive, than in normal mice.

"Perp loss promotes cancer in three different ways," Attardi said. The scientists observed the overproduction of inflammatory molecules (known to promote cancer), the increased survival of cells that should have committed suicide in response to excessive UVB and a loss of cell-cell adhesion commensurate with the loss of desmosomes.

At the same time, the mice with early stages of skin cancer continued to retain normal function of another variety of adhesion junction complex that has been observed to be dysfunctional in advanced cancer stages, such as metastasis. What the researchers have shown in this study is that the earlier loss of desmosome function is enough, by itself, to promote tumor growth.

The investigators also observed a substantial disappearance of Perp in

biopsied human squamous-cell carcinoma samples. Once again, the alternative adhesion junction complexes that have been implicated in later stages of cancer appeared to be present and functioning normally in almost all of these samples, further supporting the idea that desmosome loss due to Perp inactivation can be an early, defining event in cancer progression.

Squamous-cell cancer is the second-most common of all human skin cancers after basal-cell carcinoma, striking hundreds of thousands per year in the United States. The Attardi lab findings could be applicable to basal-cell carcinoma, too. On the order of 1 million new cases of basal-cell carcinoma, by far the most common skin cancer, are reported in the United States each year. Fortunately these cancer types have very high cure rates — largely because they're so easily spotted that tumors can be removed long before they advance to a dangerous state.

But epithelial tissues at many far less accessible sites (for example, internal organs such as esophagus and pancreas) develop cancers that are caught late — often too late for effective treatment. Most healthy epithelial cells harbor desmosomes on their surfaces, suggesting that these ubiquitous structures' depletion or dysfunction may factor into a number of different tumor types.

"We think our study may also be relevant to other cancers, such as head-and-neck cancer, which is much deadly than skin cancer," she said. More than 35,000 new head-and-neck cancer cases are diagnosed each year in the United States.

A tumor-progression marker that could be detected early might prove useful not only in diagnosing and staging tumors but also in enhancing physicians' treatment decisions. "You might use more aggressive treatment on tumors lacking Perp, but spare patients with tumors that have Perp from the most-aggressive treatments," said Attardi.

"Understanding this protein's role better may also point to new therapeutic approaches."

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